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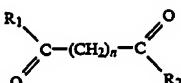
[54] **POTENT INDUCERS OF TERMINAL DIFFERENTIATION AND METHODS OF USE THEREOF**

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[57] **ABSTRACT**

The present invention provides the compound having the structure:



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[58] Field of Search 564/155, 152, 158, 160,
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wherein each of R₁ and R₂ are independently the same as or different from each other; when R₁ and R₂ are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, or thiazoleamino group; when R₁ and R₂ are different, R₁=R₃—N—R₄, wherein each of R₃ and R₄ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R₃ and R₄ bond together to form a piperidine group and R₂ is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and n is an integer from about 4 to about 8.

The present invention also provides a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells. Moreover, the present invention provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells. Lastly, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically acceptable amount of the compound above.

EA

[56] **References Cited**
U.S. PATENT DOCUMENTS

2,279,560 4/1942 Dietrich 252/47
2,279,973 4/1942 Dietrich 252/51
2,346,665 4/1944 Cupery 564/158

(List continued on next page.)

OTHER PUBLICATIONS

Marks et al., *Proc. Natl. Acad. Sci.*, vol. 86, pp.
6358-6362 (Aug. 1989).

(List continued on next page.)

17 Claims, No Drawings

1

5,369,108

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U.S. PATENT DOCUMENTS

2,895,991	7/1959	Randall et al.	564/155
3,450,673	6/1969	McKillip	528/335
3,632,783	1/1972	Stonis	264/158
3,875,301	4/1975	Windheuser	564/155
4,056,524	11/1977	Walker	564/155
4,442,305	4/1984	Weitl et al.	562/451
4,480,125	10/1984	Haas et al.	564/155
4,537,781	8/1985	Darling	564/155
4,611,053	9/1986	Sasa	528/335
4,614,815	9/1986	Cognigni et al.	500/88
4,801,748	1/1989	Murahashi et al.	564/124
4,863,967	9/1989	Hall et al.	564/150
4,882,346	11/1989	Driscoll et al.	514/389
5,055,608	10/1991	Marks et al.	560/169

OTHER PUBLICATIONS

Chun et al., *Cancer Treatment Reports*, vol. 70, pp. 991-996 (Aug. 1986).

- Reuben et al., *J. Biolog. Chem.*, vol. 253, pp. 4214-4218 (Jun. 1978).
 Tanaka et al., *Proc. Natl. Acad. Sci. (USA)*, vol. 72, pp. 1003-1006 (Mar. 1975).
 Fibach et al., *Cancer Research*, vol. 37, pp. 440-444 (Feb. 1977).
 Melloni et al., *Chem. Abs.*, vol. 109, No. 47737e (1988).
 Hozumi et al., *Int. J. Cancer*, vol. 23, pp. 119-122 (1979).
 Haces et al., *J. Med. Chem.*, vol. 30, pp. 405-409 (1987).
 Das et al., *Chem. Abs.*, vol. 101, No. 54665t (1984).
 Brown et al., *Chem. Abs.*, vol. 105, No. 75801v (1986).
 Hynes, *J. Med. Chem.*, vol. 13, No. 6, pp. 1235-1237 (1971).
 Tabernero et al., *Chem. Abs.*, vol. 98, No. 191329v (1983).
 Morrison and Boyd, *Organic Chemistry* (3rd ed. Allyn and Bacon Boston) (1973) p. 755.
 Weitl et al., *J. Org. Chem.*, vol. 46, pp. 5234-5237 (1981).